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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JOHN B. SULLIVAN and FINDLAY E. RUSSELL

Appeal 2009-002479
Application 08/405,454
Technology Center 1600

Decided:[1] June 15, 2009

Before MICHAEL R. FLEMING, *Chief Administrative Patent Judge,* JAMES T. MOORE, *Vice Chief Administrative Patent Judge,* and DONALD E. ADAMS, DEMETRA J. MILLS, SALLY G. LANE, ERIC GRIMES, and LORA M. GREEN, *Administrative Patent Judges*.

ADAMS, *Administrative Patent Judge*.

DECISION ON APPEAL

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[1] The two-month time period for filing an appeal or commencing a civil action, as recited in 37 C.F.R. § 1.304, begins to run from the decided date shown on this page of the decision. The time period does not run from the Mail Date (paper delivery) or Notification Date (electronic delivery).

This appeal under 35 U.S.C. § 134 involves claims 40-42 and 50. The only remaining pending claims, claims 54 and 55, were withdrawn from consideration as drawn to a non-elected invention (*see e.g.*, App. Br. 1). We have jurisdiction under 35 U.S.C. § 6(b).

STATEMENT OF THE CASE

This Appeal is back before the Board on remand from the Court of Appeals for the Federal Circuit, our appellate reviewing court.

The Federal Circuit found that "a prima facie case of obviousness was established [in this case] because Sullivan teaches whole antibodies for use against rattlesnake venom and Coulter teaches using Fab fragments to detect venom of a different snake." *In re Sullivan*, 498 F.3d 1345, 1351 (Fed. Cir. 2007).

Nevertheless, our appellate reviewing court found that the Board failed to give sufficient weight to Appellants' declaratory evidence. Specifically, it found that the following three pieces of evidence in the record required further consideration: (1) the Smith Declaration, which "is relevant as evidence that the prior art taught away from the claimed invention"; (2) the Sullivan Declaration, which "describes an unexpected property or result from the use of Fab fragment antivenom"; and (3) the First Russell Declaration, which "discusses why those having ordinary skill in the art expected antivenoms comprising Fab fragments to fail." *Id.* at 1352.

Accordingly, the Federal Circuit vacated the Board's March 30, 2006 Decision affirming the rejection of claims 40-42 and 50 under 35 U.S.C. § 103 as being unpatentable over the combination of Sullivan and Coulter. *See id.* at 1352-53. Therefore, we reconsider the record before us on appeal *de novo*, carefully evaluating and weighing both the evidence relied upon by

the Examiner and the objective evidence of nonobviousness provided by Appellants.

The claims are directed to an antivenom pharmaceutical composition. Claim 40 is illustrative of the subject matter on appeal and is reproduced below:

> 40. An antivenom pharmaceutical composition for treating a snakebite victim, comprising Fab fragments which bind specifically to a venom of a snake of the Crotalus genus and which are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and a pharmaceutically acceptable carrier, wherein said antivenom pharmaceutical composition neutralizes the lethality of the venom of a snake of the Crotalus genus.

The Examiner relies on the following evidence:

Stedman's Medical Dictionary 94 (23rd ed., Williams and Wilkins Co., 1976).

Smith et al., *Immunogenicity and kinetics of distribution and elimination of sheep digoxin-specific IgG and Fab fragments in the rabbit and baboon,* 36 CLIN. EXP. IMMUNOL. 384-96 (1979).

J. B. Sullivan, Jr. and F. E. Russell, *ISOLATION AND PURIFICATION OF ANTIBODIES TO RATTLESNAKE VENOM BY AFFINITY CHROMATOGRAPHY,* 25 PROC. WEST. PHARMACOL. SOC. 185-92 (1982).

Alan Coulter and Rodney Harris, *Simplified Preparation of Rabbit Fab Fragments*, 59 J. IMMUNOL. METHODS 199-203 (1983).

Appellants rely on the following evidence:

First Russell Declaration, executed April 30, 1998.

Smith Declaration, executed April 24, 1995.

Sullivan Declaration, executed September 25, 1995.

Stewart Sell, M.D., *Basic Immunology: Immune Mechanisms in Health and Disease,* 89 (ed., Elsevier, New York, NY) (1957).

Findlay E. Russell, M.D., Ph.D., *Snake Venom Poisoning* 5, 139, and 168 (ed., J.B. Lippincott Co., Philadelphia, PA) (1980).

Faulstich et al., *STRONGLY ENHANCED TOXICITY OF THE MUSHROOM TOXIN α-AMATOXIN BY AN AMATOXIN-SPECIFIC FAB OR MONOCLONAL ANTIBODY,* 26 TOXICON 491-499 (1988).

Russell, *SNAKE VENOM IMMUNOLOGY: HISTORICAL AND PRACTICAL CONSIDERATIONS,* 7 J. TOXICOL. - TOXIN REVIEWS 1-82 (1988).

Joseph Balthasar and Ho-Leung Fung, *Utilization of Antidrug Antibody Fragments for the Optimization of Intraperitoneal Drug Therapy: Studies Using Digoxin as a Model Drug,* 268 J. PHARM. EXP. THER. 734-739 (1994).

Sorkine et al., *Comparison of $F(ab')_2$ and Fab efficiency on plasma extravasation induced by Viper aspis venom*, 33 TOXICON 257 (1995).

Ownby et. al., *Levels of Therapeutic Antivenin and Venom in a Human Snakebite Victim*, 89 SOUTHERN MEDICAL JOURNAL 803-807 (1996).

Russell, *Toxic Effects of Animal Toxins,* in *Casarett and Doull's Toxicology: The Basic Science of Poisons* 801-805 (5th ed., McGraw-Hill, New York, NY) (1996).

WHO Coordination Meeting on Venoms and Antivenoms, WHO/B5/80-1292 BLG/Ven/80.1 Rev. 1 (Date unknown).

The rejections presented by the Examiner are as follows:

1. Claims 40-42 and 50 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan in view of Coulter.

2. Claims 40-42 and 50 stand rejected under 35 U.S.C. § 103 as being unpatentable over Sullivan in view of Coulter, Smith and Stedman's.

We affirm.

The combination of Sullivan in view of Coulter:

ISSUES

Given that the Federal Circuit held that a prima facie case of obviousness has been established on this record, the issue before us distills down to whether the prima facie case of obviousness over the combination of Sullivan and Coulter stands when reconsidered in view of Appellants' arguments and Declaratory evidence on this record.

FINDINGS OF FACT

FF 1. The instant application has an effective filing date of October 9, 1984.

FF 2. "A venom is a toxic substance produced by a plant or animal . . . and usually delivered through a biting or stinging act" (First Russell Declaration 3: ¶ 15). "Antivenin is a suspension of venom-neutralizing antibodies prepared from the serum of animals . . . hyperimmunized against a specific venom or venoms" (Spec. 4: 19-22; First Russell Declaration 5: ¶ 18). "[T]he terms 'antivenin' and 'antivenom' are now interchangeable" in the art (First Russell Declaration 5: ¶ 18).

FF 3. Russell declares that during envenomation, "[v]enom components are usually injected into subcutaneous tissues. Since many of the venom toxins are large, hydrophobic molecules, they are slowly released from these injection areas. This results in the 'venom depot effect' where toxins are continuously released into the systemic circulation long after the initial bite" (First Russell Declaration 9: ¶ 30).

FF 4. Russell declares that "[S]nake venoms of the family Crotalidae comprise at least 20 different compounds. In some *Crotalus sp.* snake

venoms, there may be 100 different protein fractions, 25 of which may be enzymes. Due to their complexity, the full composition of snake venoms is unknown" and "the pharmacological effects of some constituent toxins are unknown" (First Russell Declaration 4: ¶ 15-16).

FF 5. Russell declares that "[i]mmunoglobulins neutralize toxins in several ways. For example, they bind specifically to epitopes present on the toxins. In the case of a polyclonal antivenom, this may involve several epitopes present on more than one antigen" (First Russell Declaration 8-9: ¶ 28).

FF 6. At the time the invention was made the "therapeutic modality for treatment of Crotalidae envenomation [in humans] in the United States involves the intravenous administration of equine source Antivenin (Crotalidae) Polyvalent (ACP)" (Sullivan 185: 1-3; *see also* First Russell Declaration 5-6: ¶ 19 and 6: ¶ 21).

FF 7. Smith declares that "Antivenins comprising intact antibodies have been sold commercially since at least 1947. Antivenins comprising $F(ab)_2$ fragments have been sold commercially since at least 1969." (Smith Declaration 2: ¶ 7). Russell declares that "At the time of the application, the only commercially available antivenom for envenomation by North American snakes of the family Crotalidae was Antivenin (Crotalidae) Polyvalent [(ACP)] (equine origin) (Wyeth Laboratories, Philadelphia, PA)" (First Russell Declaration 5-6: ¶ 19).

FF 8. Sullivan teaches "purified antivenin polyvalent antibodies derived from horse hyperimmune antisera against venom of the Crotalus genus [(ACP)] (see Methods section, pages 185-187)" (Ans. 5). Sullivan teaches that the ACP antibodies neutralize the lethality of the venom of a snake of the Crotalus genus (Sullivan 187: 18-23).

FF 9. Russell declares that "[s]oon after the development of the first antivenoms, doctors recognized that they could elicit serum sickness, an allergic reaction to the antisera that was sometimes more deleterious than the venom. Over 75% of patients treated with ACP develop some manifestation of serum sickness" (First Russell Declaration 6: ¶ 21; *see also* Sullivan 185: 3-8).

FF 10. Sullivan teaches "that reducing the immunogenicity of polyvalent horse antivenin is an important goal, due to immune reactions that limit the clinical efficacy of antivenin preparations which contain only partially purified hyperimmune horse antisera (see page 185, first paragraph)" (Ans. 7). In this regard, Sullivan teaches that the incidence of serum sickness reactions should be significantly reduced by the removal of extraneous foreign protein (Sullivan 190: 9 - 191: 2).

FF 11. Russell declares that because "serum sickness results from immune reactions of the patient to the immunoglobulin component of the antivenom, which actually binds to the venom toxins, . . . research focused on using fragments of immunoglobulin molecules that might not provoke a[n] immune reaction" (First Russell Declaration 7: ¶ 22; *see also* Spec. 2: 38 - 3: 2 ("It is also well known in the art that the smaller F(ab) fragments are less likely to cause undesired immunogenic reactions. A general rule is that, given possession of the antibody active site, the smaller the antibody molecule the better")).

FF 12. "Sullivan does not teach a F(ab) containing antivenin" (Ans. 5). According to Russell, "[d]espite known problems with the only commercially available antisera for Crotalidae envenomation and much research since 1947, no researcher had developed an antivenom comprising

Fab fragments" (First Russell Declaration 14: ¶ 43). In this regard, Russell declares that "those of ordinary skill in the art had not progressed beyond $F(ab)_2$ fragments to the smaller Fab fragments" (*id.*). *See also*, Sullivan Declaration 3: ¶ 5 ("The development of antivenin production through the years stopped at a final product of $F(ab)_2$'s").

FF 13. Coulter teaches an anti-Australian brown snake toxin composition comprising Fab fragments that are free of Fc in a pharmaceutically acceptable carrier (PBS) (Coulter 200: 10-23; Ans. 6). Coulter teaches a method for preparing rabbit-derived Fab fragments that includes the removal of undigested immunoglobulin and Fc fragments (Coulter 200: 19-20).

FF 14. The toxin used in Coulter's study, textilotoxin, is a single toxin from the venom of the Australian brown snake (*Pseudonaja textilis*), which is not a member of the genus *Crotalidae* (First Russell Declaration 15: ¶ 46 and ¶ 47).

FF 15. Coulter teaches the use of Fab fragments to detect venom of a snake. (Coulter 201: 1-15; 202: 7-12). In this regard, Coulter teaches that higher assay sensitivity has been observed when Fab is used instead of intact IgG in immunoassays (Coulter 199: 2-3).

FF 16. Coulter teaches that a composition comprising F(ab) fragments reactive against a snake toxin is capable of neutralizing the lethality of that snake toxin in vivo (Ans. 7).

FF 17. Russell declares that at the time the invention was made, persons of ordinary skill in this art recognized that due to their small size, Fab fragments can be distributed to more parts of the body than the larger $F(ab')_2$ and intact IgG molecules (First Russell Declaration 11: ¶ 35; *see also* Spec.

21: 6-8; and Sorkine 257: 13-14 (The smaller size of Fab relative to $F(ab)_2$ results in faster diffusion and a greater volume of distribution)).

FF 18. In addition, and consistent with the statements of Russell, Smith, and Sullivan, at the time this invention was made, persons of ordinary skill in this art recognized that "Fab fragments are small enough to be removed by the renal system. Consequently they have a half-life of about 17 hours" and "are completely eliminated in only 24 to 26 hours" (First Russell Declaration 9-10: ¶ 31; Sullivan Declaration 3: ¶ 5). However, F(ab) fragments in complex with venom protein are "too large to be excreted rapidly by glomerular filtration" (Smith Declaration 2: ¶ 6; Sullivan Declaration 3: ¶ 5). The same is true of "$F(ab)_2$ fragments and whole IgG[, which] are also too large to be eliminated by the renal system . . . [and therefore] have a longer half-life, approximately 50 hours," relative to [uncomplexed] Fab fragments (First Russell Declaration 10: ¶ 32; *see also* Sullivan Declaration 5: ¶ 5).

FF 19. Faulstich teaches that "[t]oxicity in mice of α-amanitin (i.p.), followed by i.v. administration of a monoclonal antibody, is very similar to the toxicity caused by i.v. administration of the amanitin-immunoglobulin complex" (Faulstich 495: 6-8). Similarly, in Coulter's study, textilotoxin was first mixed with Fab fragments *in vitro* and then the Fab-textilotoxin complex was injected intravenously. Russell declares that "[t]his treatment with Fab fragments resulted in neutralization that was essentially equivalent to the treatment with the IgG fragments, just as one would have expected" (First Russell Declaration 16: ¶ 48). Sorkine conducted a similar experiment wherein Fab fragments were mixed with a venom of a non-Crotalidae snake prior to injection into a mouse, and they obtained results similar to those observed by Coulter (First Russell Declaration 17: ¶ 50). Sullivan also

teaches a study wherein venom and antibody are mixed prior to injection into an animal to establish the antibody's ability to protect against lethality of the venom (Sullivan 187: 18-23). Appellants also determine lethality of the toxin by injecting a complex of toxin and immunoglobulin, or fragment thereof, into an animal (Spec. 18-19).

FF 20. After Appellants' effective filing date Faulstich identified an intact antibody and its corresponding Fab fragment that were both incapable of neutralizing the toxicity of the mushroom toxin (α-amatoxin) (Faulstich 497: 18-23).

FF 21. Faulstich reports that not only were the Fab fragments unable to neutralize the toxicity of α-amatoxin in mice, but they increased the toxicity of α-amatoxin by a factor of 50 (First Russell Declaration 12: ¶ 38). According to the post-filing date Faulstich reference "[t]o our knowledge this is the first reported case where immunoglobulins or their fragments enhance rather than decrease the activity of a toxin" (Faulstich 491: Abstract). The post-filing date Balthasar reference cites Faulstich's work and states that "[t]he risk of redistributing systemic toxicity, rather than minimizing systemic toxicity, should be appreciated as a potential outcome" of the use of antibodies to neutralize the toxicity of a toxin (Balthasar 738: col. 2, ll. 3-6; First Russell Declaration 13: ¶ 40).

FF 22. Sorkine reports that when antibody fragments are not mixed with venom prior to injection a larger concentration of antibody fragments is necessary to neutralize the toxin, "Fab being five times more effective than $F(ab')_2$" (Sorkine). In addition, Sorkine's

> data showed firstly that the *in vitro* neutralization of the venom by immunoglobulin fragments does not reflect their *in vivo* efficiency. Secondly, Fab was considerably more effective than

> $F(ab')_2$ in reducing CPI [capillary permeability increase] induced by venom. One explanation is the different kinetics of these fragments. The smaller size of Fab results in faster diffusion and a greater volume of distribution.

(Sorkine 257: 11-14.)

FF 23. Smith discusses a post-filing date clinical study of the treatment of *Vipera berus* envenomation with the purified ovine F(ab) fragment TAb001 and "conventional" $F(ab)_2$ antivenom (Smith Declaration 2: ¶ 11-13). Smith declares that

> TAb001 appears to be equally effective as the conventional antivenom in reducing the occurrence of extensive edema and severe anemia as well as shortening hospital stay. Moreover, to date, no allergic events, suggesting an immediate or delayed hypersensitivity response, have been observed after administration of TAb001, whereas 10% of those given conventional antivenom had allergic side-effects.

(Smith Declaration 5-6: ¶ 13.)

FF 24. Appellants' Specification discloses a comparison of the ability of intact ACP antibody and Fab fragments to protect against snake venom (Spec. 18-23). Appellants disclose that while the dosage "will be adjusted to suit the particular circumstances of the envenomation" the data indicates that both F(ab) fragments and intact IgG "can be used in the treatment of human snake bite victims" (Spec. 23).

PRINCIPLES OF LAW

The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) secondary considerations of

nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

"[D]uring examination proceedings, claims are given their broadest reasonable interpretation consistent with the specification." *In re Hyatt*, 211 F.3d 1367, 1372 (Fed. Cir. 2000). "[A] claim preamble has the import that the claim as a whole suggests for it." *Bell Communications Research, Inc. v. Vitalink Communications Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995). However, where a patentee defines a structurally complete invention in the claim body and uses the preamble only to state a purpose or intended use for the invention, the preamble is not a claim limitation. *Id.*; *Rowe v. Dror*, 112 F.3d 473, 478 (Fed. Cir. 1997).

Obviousness is determined from the context of a person of ordinary skill in the art at the time the invention was made. "[T]he level of skill in the art is a prism or lens through which a judge, jury, or the Board views the prior art and the claimed invention. This reference point prevents these factfinders from using their own insight or, worse yet, hindsight, to gauge obviousness." *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001), (citation omitted). Therefore, the evidence of record must be viewed through the lens of a person of ordinary skill in the art with consideration of common knowledge and common sense. *Graham*, 383 U.S. at 17-18; *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1367 (Fed. Cir. 2006).

Therefore, it is proper to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR Int'l Co. v. Teleflex Inc*, 550 U.S. 398, 418 (2007). *See also id.* at 421 ("A person of ordinary skill is also a person of ordinary creativity, not an automaton.").

"In determining whether obviousness is established by combining the teachings of the prior art, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d 1573, 1581 (Fed. Cir. 1995) (internal quotations omitted). Thus, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. Similarly, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417.

> "[W]hen a prima facie case is made, the burden shifts to the applicant to come forward with evidence and/or argument supporting patentability." *In re Glaug,* 283 F.3d 1335, 1338 (Fed. Cir. 2002). Rebuttal evidence is "merely a showing of facts supporting the opposite conclusion." *In re Piasecki,* 745 F.2d 1468, 1472 (Fed. Cir. 1984). . . . When a patent applicant puts forth rebuttal evidence, the Board must consider that evidence. *See In re Soni,* 54 F.3d 746, 750 (Fed. Cir. 1995) (stating that "all evidence of nonobviousness must be considered when assessing patentability"); *In re Sernaker,* 702 F.2d 989, 996 (Fed. Cir. 1983) ("If, however, a patent applicant presents evidence relating to these secondary considerations, the board must always consider such evidence in connection with the determination of obviousness.").

In re Sullivan, 498 F.3d at 1351. "When prima facie obviousness is established and evidence is submitted in rebuttal, the decision-maker must start over." *In re Rinehart*, 531 F.2d 1048, 1052 (CCPA 1976); *In re Hedges*, 783 F.2d 1038, 1039 (Fed. Cir. 1986) ("If a prima facie case is made in the first instance, and if the applicant comes forward with

reasonable rebuttal, whether buttressed by experiment, prior art references, or argument, the entire merits of the matter are to be reweighed").

Nevertheless, although secondary considerations must be taken into account, they do not necessarily control the obviousness conclusion. *Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). Instead, evidence of secondary considerations are but a part of the "totality of the evidence" that is used to reach the ultimate conclusion of obviousness. *Kansas Jack, Inc. v. Kuhn*, 719 F.2d 1144, 1151 (Fed. Cir. 1983). The weight of secondary considerations may be insufficient to override a determination of obviousness based on primary considerations. *Ryko Mfg. Co. v. Nu-Star, Inc*, 950 F.2d 714, 719 (Fed. Cir. 1991). For example, a long-felt need must not have been satisfied by another before the invention by applicant. *Newell*, 864 F.2d at 768 ("[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved.").

Additionally,

> In order for a showing of "unexpected results" to be probative evidence of non-obviousness, it falls upon the applicant to at least establish: (1) that there actually is a difference between the results obtained through the claimed invention and those of the prior art . . .; and (2) that the difference actually obtained would not have been expected by one skilled in the art at the time of invention.

In re Freeman, 474 F.2d 1318, 1324 (CCPA 1973) (citations omitted).

Therefore, all of the evidence must be considered under the *Graham* factors before reaching our obviousness determination.

ANALYSIS

The claims stand or fall together (App. Br. 4). Accordingly, we limit our discussion to representative independent claim 40. 37 C.F.R. § 41.37(c)(1)(vii). Claim 40 is drawn to an antivenom pharmaceutical composition for treating a snakebite victim. The claimed composition comprises:

1. Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and
2. a pharmaceutically acceptable carrier.

Claim 40 also places the following two additional restrictions on the claimed composition:

a. the Fab fragments are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and
b. the composition neutralizes the lethality of the venom of a snake of the Crotalus genus.

Having defined a structurally complete invention in the body of the claim, we conclude that the recitation of the intended use of the composition "for treating a snakebite victim" as it appears in the preamble of claim 40 does not represent a limitation in this claim. *Rowe v. Dror*, 112 F.3d at 478.

Sullivan teaches an intact horse-derived polyvalent antibody (ACP), or a purified form thereof, that specifically binds to a venom of a snake of the Crotalus genus (FF 8). ACP was the therapeutic modality for treatment of crotalidae envenomation in the United States at the time this invention was made (FF 6). ACP neutralizes the lethality of the venom of a snake of the Crotalus genus (FF 8).

Coulter teaches an anti-Australian brown snake toxin composition comprising Fab fragments that are free of Fc in a pharmaceutically

acceptable carrier (PBS) (FF 13). Coulter teaches that the use of Fab fragments in assays results in a higher sensitivity over the use of intact immunoglobulin molecules (FF 15). Coulter also teaches that Fab fragments retain the ability to neutralize the lethality of snake toxin (FF 16).

Taken together a person of ordinary skill in the art would have recognized that the use of Fab fragments of Sullivan's polyvalent antibody would enhance the sensitivity of Sullivan's antibodies in assays. "[I]f a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 550 U.S. at 417. Thus, it would have been prima facie obvious to follow Coulter's methodology to prepare Fab fragments of Sullivan's polyvalent antibody in a pharmaceutically acceptable carrier for use in assays including enzyme immunoassays. Appellants do not dispute and therefore concede that the Fab fragment composition taught by the combination of Sullivan and Coulter would be expected to be essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies (*see* FF 13).

For the foregoing reasons a person of ordinary skill in this art, at the time the invention was made, who followed the combined teachings of Sullivan and Coulter would have had a reasonable expectation of success in obtaining a composition that (a) is essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies and (b) neutralizes the venom of a snake of the Crotalus genus.

Accordingly, the combination of Sullivan and Coulter made obvious a composition that comprises:

1. Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and
2. a pharmaceutically acceptable carrier.

In addition, the combination of Sullivan and Coulter made obvious

a. Fab fragments that are essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies, and
b. a composition that neutralizes the lethality of the venom of a snake of the Crotalus genus.

Therefore, the combination of Sullivan and Coulter made obvious a composition that neutralizes the lethality of the venom of a snake of the Crotalus genus comprising Fab fragments that specifically bind to a venom of a snake of the Crotalus genus, which are essentially free from contaminating Fc, and a pharmaceutically acceptable carrier.

For their part Appellants do not dispute that the combination of Sullivan and Coulter teaches a composition comprising Fab fragments in a pharmaceutically acceptable carrier for use in assays, such as enzyme immuno-assays (*see e.g.*, FF 15). Instead, Appellants contend that their intended use statement "for treating a snakebite victim" in combination with the claimed requirement that the composition neutralizes the lethality of the venom of a snake of the Crotalus genus *requires* "the Fab fragments [to] exhibit a pharmaceutical activity" (App. Br. 5). While we agree that the Fab component of the claimed composition must neutralize the lethality of the venom of a snake of the Crotalus genus, there is no requirement in claim 40 that this composition be used pharmaceutically, as opposed to its use in performing *in vitro* assays.

Nevertheless, Appellants contend that the "requirement that the antivenom pharmaceutical composition for treating a snakebite victim

comprising Fab fragments neutralizes the lethality of the venom of a snake of the Crotalus genus renders the claims patentable" (*id.*). In support of this contention Appellants direct attention to the First Russell Declaration, the Sullivan Declaration, and the Smith Declaration. Accordingly, faced with Appellants' arguments and Declarations, we reweigh the entire merits of the record before us on appeal. *In re Hedges*, 783 F.2d at 1039. In doing so, we seek to determine, *inter alia*, whether the composition made obvious by the combination of Sullivan and Coulter would have had the same properties as the composition set forth in Appellants' claim 40 – e.g., the ability to treat a snakebite victim with a composition comprising Fab fragments that neutralize the lethality of the venom of a snake of the Crotalus genus (App. Br. 5).

Sullivan teaches an intact horse-derived polyvalent antibody that specifically binds to and neutralizes the lethality of the venom of a snake of the Crotalus genus (FF 8). Sullivan recognizes, however, that immune reactions (such as serum sickness) limit the clinical efficacy of the intact horse derived antibody as an antivenom (FF 10). In this regard, Sullivan teaches that the incidence of serum sickness reactions should be significantly reduced by the removal of extraneous foreign protein (*id.*). Likewise, it was known in the art at the time this invention was made that Fab fragments are less likely to cause undesired immunogenic reactions (FF 11). Coulter teaches a method of producing Fab fragments that are free of Fc and retain their ability to neutralize the toxicity of a snake venom toxin (FF 13 and 16).

Therefore, at the time the invention was made, a person of ordinary skill in this art who followed the combined teachings of Sullivan and Coulter would have had a reasonable expectation of success in obtaining a

composition that (a) is essentially free from contaminating Fc as determined by immunoelectrophoresis using anti-Fc antibodies and (b) neutralizes the venom of a snake of the Crotalus genus. This composition would comprise (1) Fab fragments which bind specifically to a venom of a snake of the Crotalus genus, and (2) a pharmaceutically acceptable carrier. In addition, a person of ordinary skill in this art would have recognized that Fab fragments are less likely to cause undesired immunogenic reactions. Therefore, a person of ordinary skill in this art would have utilized this Fab fragment composition to treat snake bite victims with a reasonable expectation of success given that the polyvalent antibodies taught by Sullivan are based on "the only commercially available antivenom for envenomation by North American snakes of the family Crotalidae" (FF 7) and Coulter teaches that Fab fragments retain their intact parent immunoglobulin's ability to neutralize the lethality of snake venom toxin (FF 16). The test for obviousness is "what the combined teachings of the references would have suggested to those of ordinary skill in the art." *In re GPAC Inc.*, 57 F.3d at 1581. The study discussed in Smith's Declaration and the experimental data in Appellants' Specification confirm the reasonable expectation of success a person of ordinary skill in the art would have had in combining the teachings of Sullivan and Coulter (FF 23 and 24).

Accordingly, we are not persuaded by Appellants' contention that "[t]here was no suggestion in the prior art that Fab fragments could be used to create an antivenom pharmaceutical composition for treating a snakebite victim that would neutralize the lethality of the venom of a snake of the Crotalus genus" (App. Br. 6). For the same reasons we are not persuaded by Appellants' contention that the

> Development of antivenoms comprising antibody fragments [was] halted at the larger $F(ab)_2$ fragments because researchers expected the smaller Fab fragments to be even less effective than $F(ab)_2$ fragments, which appeared to some to be less effective than whole antibody, for several reasons. [First Russell Decl. at ¶ 26; Sullivan Decl. at ¶ 5; Smith Decl. at ¶ 9.]

(App. Br. 8.) On this record, Coulter provides the evidence necessary to establish that Fab fragments are effective in neutralizing the toxicity of snake venom (FF 16). In short, the evidence of record establishes that those of ordinary skill in this art would have reasonably expected that the Fab fragments of Sullivan's polyvalent antibody would not only neutralize the toxicity of snake venom in vivo, but would also provide the additional advantage of reducing serum sickness (*see e.g.*, FF 11). Accordingly, we are not persuaded by Appellants' contention that the use of Fab fragments to neutralize snake venom in vivo would have been unexpected by those of ordinary skill in the art. *See In re Freeman* 474 F.2d at 1324 (to be probative evidence of non-obviousness unexpected results must not have been expected by those of ordinary skill in the art).

Appellants contend that Fab fragments cannot (1) "stearically [sic] hinder[ ] the venom antigen from binding to its active site"; (2) "form cross-linked complexes and precipitate the antigens"; or (3) neutralize venom toxins that continue to be released from the injection site long after the bite because Fab fragments have a half-life of about 17 hours (App. Br. 8-9). We are not persuaded.

There is no evidence on this record to suggest that an immunoglobulin must sterically hinder the binding of the venom to its active site or cross-link and precipitate the venom toxin in order to neutralize the lethality of the toxin. Notwithstanding Appellants' contentions to the contrary, Coulter

teaches that Fab fragments are effective in neutralizing the toxicity of snake venom (FF 16).

We are also not persuaded by Appellants' contention regarding the relationship between the "venom depot effect" (FF 3) and the *in vivo* half-life of circulating antibodies or Fab fragments thereof (FF 18). Initially, it cannot be overstated that the claimed invention is drawn to a composition, not a method of treatment. That said, to the extent that the claimed composition is intended to be used to treat a snake bite, there is nothing in Appellants' claimed invention that would preclude the administration of additional doses of a Fab-based antivenom to maintain the concentration of circulating Fab fragments in the patient at a level that will address the "venom depot effect."

For the foregoing reasons we are not persuaded by Appellants' contentions regarding the long-felt but unsatisfied need in the art to develop antivenoms comprising Fab fragments (App. Br. 9). Appellants' evidence suggests that prior to Coulter, no one in this art took the step toward producing a Fab based antivenom (FF 12). However, prior to Appellants' effective filing date Coulter took that step and taught that Fab fragments are effective in neutralizing the toxicity of snake venom (FF 16). In doing so, Coulter supplied the key element required to satisfy the long-felt need that Appellants contend was recognized in this art (App. Br. 9). *Newell*, 864 F.2d at 768 ("[O]nce another supplied the key element, there was no long-felt need or, indeed, a problem to be solved."). As a result, the composition set forth in Appellants' claim 40 is nothing more than a composition that would have resulted from following the combined teachings of Sullivan and Coulter. Accordingly, we are not persuaded by Appellants' contentions

regarding long-felt need since any such need was satisfied by Coulter prior to Appellants' earliest effective filing date.[2]

Appellants contend that at the time the invention was made "those of ordinary in the skill in the art believe[d] that Fab fragments . . . 'would **increase** the toxicity of the venom' by redistributing and concentrating its toxins. [Sullivan Decl. at ¶ 5(b) (original emphasis), ¶ 13; Russell Decl. at ¶ 33.]" (App. Br. 10 (alteration original)). Appellants contend that "[t]his taxi effect was a reason why those of ordinary skill in the art did not progress beyond the known $F(ab)_2$ fragments to the smaller Fab fragments. [Sullivan Decl. at ¶ 7]" (*id.* (alteration original)). To support this contention Appellants rely on the post-filing date Faulstich reference. We are not persuaded.

Faulstich teaches that both intact antibody against the mushroom toxin (α-amatoxin) and Fab fragments thereof are incapable of neutralizing the toxicity of the toxin (FF 20). Instead, Faulstich found that the Fab fragments increased the toxicity of the α-amatoxin (FF 21). In this regard, the post-filing date Faulstich reference reports that "[t]o our knowledge this is the first reported case where immunoglobulins or their fragments enhance rather than decrease the activity of a toxin" (*id.*). While the post-filing date Balthasar reference cites Faulstich, it adds nothing more than a comment that "[t]he risk of redistributing systemic toxicity, rather than minimizing

[2] We recognize the argument Appellants made in their Brief to our appellate reviewing court regarding commercial success. 2006 WL 3243570 50-51; 2006 WL 4385792 17-18. We note, however, Appellants provided no evidence or argument relating to commercial success in any of their briefings to this Board.

systemic toxicity, should be appreciated as a potential outcome of the proposed approach" (FF 21; App. Br. 12).

Accordingly, both Faulstich and Balthasar fail to support Appellants' contention that, at the time their invention was made, those of ordinary skill in this art were concerned that Fab fragments of antibodies, *effective in neutralizing the toxicity of toxins*, would increase the toxicity of the toxin due to what Appellants refer to as a "taxi-effect."

In contrast to Faulstich, the combination of references relied upon on this record teach antibodies and Fab fragments that *are effective in neutralizing the toxicity of a toxin*. Specifically, Coulter teaches that Fab fragments are effective in neutralizing the toxicity of snake venom (FF 16). As Appellants admit, the post-filing date Sorkine reference conducted a study similar to Coulter's and obtained similar results (App. Br. 13).

In sum, we have not been directed to sufficient evidence on this record to support Appellants' intimation that Fab fragments derived from antibodies that were *capable of neutralizing the toxicity of a toxin*, as taught by the combination of Sullivan and Coulter, would increase - rather than neutralize - the toxicity of a toxin.

Nevertheless, Appellants contend that Coulter did not teach the treatment of "envenomation with their Fab fragments," rather Coulter pre-mixed the Fab fragments with the toxin and then injected the complex into mice to determine if the Fab fragments were capable of protecting the mouse from the effects of the toxin (App. Br. 13). Appellants contend that "[s]ince the Fab-textilotoxin mixture was first mixed *in vitro* and then injected intravenously, the Fab did not have the opportunity to redistribute and concentrate the textilotoxin in high blood flow parts" (*id.*). Further,

Appellants contend that Sorkine's post-filing date teachings establish "that one would not have expected Coulter et al.'s in vitro neutralization results to predict the effectiveness of antivenoms comprising Fab fragments in vivo" (App. Br. 14 (emphasis removed)). We are not persuaded.

Sorkine teaches that if antibody fragments are not mixed with venom prior to injection then a larger concentration of antibody fragments is necessary to neutralize the venom (FF 22). This is a dosage issue well within the purview of a person of ordinary skill in the art at the time the invention was made. Further, Sorkine supports rather than refutes the conventional knowledge in the art at the time the invention was made, by teaching that due to their faster diffusion and a greater volume of distribution Fab fragments would be more effective at neutralizing venom than intact antibody and $F(ab)_2$ fragments (*Cf.* FF 22 and FF 17).

Despite Appellants' contention to the contrary, Coulter utilized what appears to have been an art accepted procedure for predicting efficacy of antivenom at the time of the claimed invention. In this regard, we recognize that Appellants utilize a similar procedure to determine efficacy of antivenom as does Sullivan (FF 19). Further, according to Faulstich the toxicity of a toxin administered i.p. followed by the i.v. administration of a monoclonal antibody "is very similar to the toxicity caused by i.v. administration of the amanitin-immunoglobulin complex" (*id.*). Therefore, despite Appellants' contention to the contrary, Faulstich confirms that methodology utilizing a pre-formed complex of a toxin and an antibody or fragment thereof is predictive of the separate administration of the two compounds (*id.*).

In addition, Appellants contend that since Coulter's Fab fragments were directed to a single toxin in the venom of the Australian brown snake "the Examiner is incorrect in attempting to extrapolate Coulter['s] . . . results with Fab fragments to a single snake venom toxin to the results that would have been expected with Fab fragments to an entire snake venom" (App. Br. 14). Accordingly, Appellants contend that "[s]ince one of ordinary skill in the art would not have expected Coulter['s] . . . results with Fab fragments to a single venom toxin to predict what would occur with an antivenom comprising Fab fragments to an entire venom, any rejection relying upon the Coulter *et al.* reference must fail" (App. Br. 14-15). We are not persuaded.

Notwithstanding Appellants' contention to the contrary, the prior art suggests the use of Coulter's methodology to prepare Fab fragments of Sullivan's polyvalent antibody. Thus, the result would not be a Fab fragment directed toward a single toxin, but instead would be antivenin polyvalent Fab fragments directed against a plurality of toxins in the venom of a snake in the Crotalus genus (FF8).

We recognize the Sullivan Declaration's discussion of equine-derived IgG(T) antibodies such as those taught by Sullivan (Sullivan Declaration 4: ¶ 6). The Sullivan Declaration states that "[t]he early success of equine-derived antivenin containing IgG(T) antibody was due to the nature of the IgG(T) antibody, which has an extra disulfide bond . . .[, which] allows IgG(T) to bind with enhancement to repeating protein antigens" (*id.*). The Sullivan Declaration states that while IgG(T) and its corresponding $F(ab)_2$ fragment would both contain this "extra disulfide bond," a "F(ab) would <u>not</u>, thus diminishing clinical efficacy" (Sullivan Declaration 4-5: ¶ 6). We are not persuaded.

Coulter teaches rabbit-derived Fab fragments, which do not contain the "extra disulfide bond" found in IgG(T) antibodies, that were effective in neutralizing the toxicity of snake venom thereby demonstrating that the "extra disulfide bond" is unnecessary to neutralize the toxicity of snake venom (FF 16).

CONCLUSIONS OF LAW

For the foregoing reasons, the conclusion of obviousness over the combination of Sullivan and Coulter stands when reconsidered in view Appellants' arguments and Declaratory evidence on this record.

The rejection of claim 40 under 35 U.S.C. § 103 as being unpatentable over the combination of Sullivan and Coulter is affirmed. Claims 41, 42, and 50 fall together with claim 40.

The rejection of claims 40-42 and 50 under 35 U.S.C. § 103 as being unpatentable over the combination of Sullivan, Coulter, Smith, and Stedman's is affirmed for the reasons discussed above. Smith and Stedman's are cumulative.

TIME PERIOD FOR RESPONSE

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED

cdc

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